A Novel Synthetic Methods for \( \alpha \)-Amino Acids from Allyl Ethers via N- Allylcarbamates

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(Received September 14, 2000)

Protected \( \alpha \)-Phenyl glycine 17 and phenylalanine 18 and 19 have been synthesized through an efficient three-step sequence from the corresponding allyl ethers 5, 7, and 10. The key intermediate in this synthesis is the corresponding allylic amines prepared by reaction of allyl ethers with chlorosulfonyl isocyanate.

Key words: \( \alpha \)-Amino acids, Chlorosulfonyl isocyanate (CSI), Allyl ethers, N-Allylcarbamates, \( \alpha \)-Phenylglycine, Phenylalanine.

INTRODUCTION

Proteinogenic and non-proteinogenic \( \alpha \)-amino acids are valuable starting materials for the construction of biologically active natural products and biologically selective and degradable drugs. Therefore, much attention has been paid to the development of concise and flexible synthetic approaches to \( \alpha \)-amino acids, allowing facile incorporation of functional groups and structural variability. Among the approaches reported in this field, Strecker amino synthesis (Williams, 1989), Ugi reaction (Ugi et al., 1982) and reductive amination of keto acid (Harada et al., 1985) are representative methods for the synthesis of \( \alpha \)-amino acids. Oxazolone route synthesis (Rao et al., 1975), alkylation of glycine enolates, electrophilic amination of amide or ester enolate (Oppolzer et al., 1988), alkylation of diacyliminium (Mooiweer et al., 1989) and halogenation of enolates followed by nucleophilic substitution of the halogen also have been used (Barrett et al., 1998). Another method used widely for synthesis of \( \alpha \)-amino acids is the oxidation of double bond in protected various allylic amines which are fundamental building blocks in organic chemistry (Hayashi et al., 1989).

Recently we reported upon a novel synthetic method for N-allylcarbamates from cinnamyl alkyl ethers using chlorosulfonyl isocyanate (CSI) (Kim et al., 2000). N-Allylcarbamates are a protected form of allylic amines and the carbamates, in particular can be used as protective groups for amino acids to minimize racemization in peptide synthesis (Greene et al., 1999). In connection with these studies, we now report the novel synthetic methods for \( \alpha \)-amino acids from allyl ethers via N-allylcarbamates (Scheme 1).

![Scheme 1. Synthetic approach to \( \alpha \)-amino acids from allyl ethers](image)

MATERIALS AND METHODS

Commercially available reagents were used without additional purification unless otherwise stated. All anhydrous solvents were distilled over CaH\(_2\) or P\(_2\)O\(_5\) or Na/benzophenone prior to reaction. All reactions were performed under an inert atmosphere of nitrogen or argon. Melting points were measured on a Gallenkamp melting point apparatus and were not corrected. Nuclear magnetic resonance spectra (\(^1\)H, and \(^{13}\)C NMR) were recorded on a Varian Unity Inova 500 MHz spectrometer and chemical shifts are reported as parts per million (ppm) from the internal standard, tetramethylsilane (TMS). Resonance pattern are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation b is used to indicate a broad signal. Coupling constants (\(J\)) are reported in hertz (Hz). IR spectra were recorded on a Nicolet 205 Infrared spectrophotometer and reported as cm\(^{-1}\). Thin layer chromatography was
carried out using plates coated with Kieselgel 60F254 (Merck). Flash column chromatography was carried out on silica gel 60 (230-400 mesh, Merck).

**General procedure for the synthesis of cinnamyl methyl methyether (5)**

To a solution of cinnamyl alcohol (4) (0.5 g, 3.73 mmol) in THF (15 ml) was added NaH (60%, 0.22 g, 5.59 mmol, 1.5eq). The reaction mixture was warmed to 45°C under N2 and CH3I (0.35 ml, 5.59 mmol, 1.5eq) was added dropwise. The reaction mixture was stirred at 45~50°C for 1h and cooled to room temperature. H2O (10 ml) was added and the solution was extracted with EtOAc (20 ml). The organic layer was washed with H2O and brine. The organic was dried over MgSO4 and concentrated. The residue was purified by column chromatography (EtOAc:Hexane=1:15) to afford 0.513 g (92.9%) of 5 as a colorless oil. Rf: 0.45 (EtOAc:hexane=1:6); 1H NMR (500MHz, CDCl3): δ 7.45-7.43 (m, 2H), 7.37-7.34 (m, 2H), 7.30-7.27 (m, 1H), 6.65 (d, 1H, J=16Hz), 6.33 (d, 1H, J=16Hz, 6Hz), 4.13 (d, 2H, J=6Hz), 3.43 (s, 3H); 13C NMR (125MHz, CDCl3): 137.44, 133.15, 129.30, 128.41, 127.21, 126.68, 73.82, 58.72; IR (neat): cm⁻¹ 3059, 2821, 1450, 1380.

**Methyl 4-phenylbut-2-enyl ether (7)**

4-Phenylbut-2-en-1-ol (6) (Rose et al., 1974) was converted to 7 as a colorless oil in 82.2% yield. Rf: 0.34 (EtOAc:hexane=1:15); 1H NMR (500MHz, CDCl3): δ 7.30-7.28 (m, 2H), 7.21-7.20 (m, 3H), 5.88 (dt, 1H, J=15Hz, 6Hz), 5.64 (dt, 1H, J=15Hz, 6Hz), 3.91 (d, 2H, J=6Hz), 3.41 (d, 2H, J=6Hz), 3.34 (s, 3H); 13C NMR (125MHz, CDCl3): δ 140.69, 133.80, 129.30, 129.15, 128.32, 126.81, 73.70, 58.56, 39.45; IR (neat): cm⁻¹ 3027, 2826, 1453.

**1,4-Diphenylbut-2-enyl methyl ether (10a)**

To a solution of 4-phenylbut-2-en-1-ol (6) (1.6 g, 10.80 mmol) in CH2Cl2 (40 ml) was added Celite and PCC (3.49 g, 16.19 mmol). The reaction mixture was stirred at room temperature for 2h under N2 and the solvent was concentrated. The result oil was dissolved in EtO and filtered through Celite. The solvent was removed and the oil obtained was redissolved in EtO (9 ml) and cooled to -20°C under N2. PhMgBr (3.0 M solution in Et2O, 2.92 ml, 10.51 mmol) was added dropwise below -10°C. The solution was stirred at 0-5°C for 1h, quenched with s-NH4Cl, then extracted with EtO (20 ml). The organic layer was separated and washed with H2O and brine. The organic was dried over MgSO4 and concentrated. The residue was purified by column chromatography (EtOAc:Hexane=1:6) to afford 1.430 g (59.1%) of 1,4-diphenylbut-2-en-1-ol (9) as a pale yellow oil.

9 was converted to 10a as a colorless oil in 78.4% yield. Rf: 0.38 (EtOAc:hexane=1:15); 1H NMR (500MHz, CDCl3): δ 7.38-7.27 (m, 7H), 7.23-7.18 (m, 3H), 5.88 (dt, 1H, J=15Hz, 6.5Hz), 5.67 (ddt, 1H, J=15Hz, 7Hz, 3.5Hz), 4.64 (d, 1H, J=7Hz), 3.42 (dd, 2H, J=6Hz, 3.5Hz), 3.33 (s, 3H); 13C NMR (125MHz, CDCl3): δ 154.02, 140.69, 132.82, 132.68, 129.30, 129.16, 128.27, 127.46, 126.82, 84.89, 57.01, 39.43; IR (neat): cm⁻¹ 3029, 2931, 1452.

**Benzyl 1,4-diphenylbut-2-enyl ether (10b)**

To a solution of 9 (0.6 g, 2.68 mmol) in THF (16 ml), DMF (4 ml) was added NaH (60%, 0.16 g, 4.01 mmol) at 0°C. BnBr (0.38 ml, 4.01 mmol) was added dropwise under N2. The reaction mixture was stirred at room temperature for 12 h. H2O (10 ml) was added and the solution was extracted with EtOAc (20 ml). The organic layer was washed with H2O and brine. The organic was dried over MgSO4 and concentrated. The residue was purified by column chromatography (EtOAc:Hexane=1:30) to afford 0.570 g (67.8%) of 10b as a colorless oil. Rf: 0.32 (EtOAc:hexane=1:15); 1H NMR (500MHz, CDCl3): δ 7.45-7.28 (m, 12H), 7.26-7.24 (m, 3H), 5.92 (dt, 1H, J=15Hz, 6.5Hz), 5.78 (dd, 1H, J=15Hz, 7Hz), 4.91 (dt, 1H, J=7Hz), 4.58 (t, 2H, J=5Hz), 3.47 (d, 2H, J=6Hz); 13C NMR (125MHz, CDCl3): δ 142.24, 140.78, 139.26, 139.03, 132.76, 129.21, 129.11, 128.41, 127.68, 126.84, 82.74, 70.75, 39.50; IR (neat): cm⁻¹ 3062, 3030, 1680, 1451.

**General procedure for the synthesis of methyl N-(1-phenylallyl)carbamate (11) and methyl N-cinnamylcarbamate (12)**

To a suspension of Na2CO3 (0.56 g, 3.54 mmol, 2.25 eq) in anhydrous CH2Cl2 (7 ml) was added CSI (0.31 ml, 3.54 mmol, 1.5eq) and a solution of cinnamyl methyl ether (5) (0.35 g, 2.36 mmol) in CH2Cl2 (3 ml) at 20°C under N2. The reaction mixture was stirred at 20°C for 30 min, quenched with H2O (10 ml), then extracted with EtOAc (5 ml x 2). The organic layer was added to a solution of Na2SO3 (25%) and KOH (10%) and the solution was stirred at room temperature for overnight. The organic layer was separated and washed with H2O and brine. The organic was dried over MgSO4 and concentrated. The residue was purified by column chromatography (EtOAc:Hexane=1:6) to afford 0.107 g (23.7%) of 11 as a white solid and 0.288 g (63.8%) of 12 as a white solid.

**Methyl N-(1-phenylallyl)carbamate (11)**

Rf: 0.37 (EtOAc:hexane=1:3); 1H NMR (500MHz, CDCl3): δ 7.36-7.26 (m, 5H), 6.04-5.97 (m, 1H), 5.38-5.30 (bs, 1H), 5.24 (dd, 1H, J=10Hz, 1.5Hz), 5.23 (dd, 1H, J=16.5Hz, 1.5Hz), 5.10-5.00 (bs, 1H), 3.68 (s, 3H); 13C NMR (125MHz, CDCl3): δ 156.91, 141.41, 138.35, 129.43, 128.38, 127.71, 116.45, 57.73, 52.96; IR (CH2Cl2): cm⁻¹ 3320, 1701, 1531, 1243; mp: 45~48°C.
Methyl N-(1-benzylallyl)carmbate (13) and Methyl N-(4-phenylbut-2-eny1)carbamate (14)

4-Phenylbut-2-enyl methyl ether (7) was converted to 13 as a colorless in 33.2% and 14 as a white solid in 36.4% yield.

Methyl N-(1-benzylallyl)carmbate (13)

RI: 0.39 (EtOAc:hexane=1:5); 1H NMR (500 MHz, CDCl3): δ 7.32-7.18 (m, 5H), 5.84-5.78 (m, 1H), 5.12 (dt, 1H, J=17Hz, 1.5Hz), 5.11 (dt, 1H, J=12Hz, 1.5Hz), 4.70-4.60 (br, 1H), 4.55-4.45 (br, 1H), 3.63 (s, 4H), 2.86 (d, 2H, J=6.5Hz); 13C NMR (125 MHz, CDCl3): δ 157.01, 138.48, 137.77, 130.21, 129.11, 127.33, 115.72, 54.62, 52.83, 42.06; IR (nujol): cm⁻¹ 3333, 1693, 1539, 1255.

Methyl N-(4-phenylbut-2-eny1)carbamate (14)

RI: 0.32 (EtOAc:hexane=1:5); 1H NMR (500 MHz, CDCl3): δ 7.31-7.28 (m, 2H), 7.22-7.16 (m, 3H), 5.77 (dt, 1H, J=15Hz, 6.5Hz), 5.53 (dt, 1H, J=15Hz, 5Hz), 4.80-4.70 (bs, 1H), 3.80-3.75 (bs, 1H), 3.69 (s, 3H), 3.36 (d, 2H, J=6.5Hz); 13C NMR (125 MHz, CDCl3): δ 157.58, 140.64, 132.34, 129.24, 128.61, 128.22, 126.87, 52.82, 43.49, 39.30; IR (nujol): cm⁻¹ 3352, 1695, 1462, 1390; mp: 60–61°C.

Methyl N-(1-benzylcinnamyl)carmbate (15)

1,4-Diphenylbut-2-enyl methyl ether (10a) was converted to 15 as a white solid in 74.1% yield. RI: 0.40 (EtOAc:hexane=1:3); 1H NMR (500 MHz, CDCl3): δ 7.39-7.21 (m, 10H), 6.47 (dd, 1H, J=16Hz, 1Hz), 6.14 (dd, 1H, J=16Hz, 6Hz), 4.80-4.75 (bs, 1H), 4.70-4.60 (bs, 1H), 3.68 (s, 3H), 2.96 (d, 2H, J=6.5Hz), 3.70 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 156.99, 137.73, 137.32, 131.15, 130.30, 129.20, 128.34, 127.39, 127.20, 54.39, 52.92, 42.49; IR (CH2Cl2): cm⁻¹ 3318, 1690, 1537, 1284; mp: 113–115°C.

Benzy1 N-(1-benzylcinnamyl)carmbate (16)

1,4-Diphenylbut-2-enyl benzy1 ether (10b) was converted to 16 as a white solid in 70.4% yield. RI: 0.31 (EtOAc:hexane=1:6); 1H NMR (500 MHz, CDCl3): δ 7.34-7.21 (m, 15H), 6.46 (d, 1H, J=16Hz), 6.14 (dd, 1H, J=16Hz, 6Hz), 5.10 (s, 2H), 4.90-4.80 (bs, 1H), 4.75-4.65 (bs, 1H), 2.97 (d, 2H, J=6.5Hz); 13C NMR (125 MHz, CDCl3): δ 156.32, 137.68, 137.29, 131.24, 130.27, 129.25, 128.83, 128.34, 127.39, 127.13, 67.47, 54.46, 42.47; IR (CH2Cl2): cm⁻¹ 3324, 1693, 1531, 1256; mp: 102-104°C.

General procedure for the synthesis of N-methoxycarbonyl α-phenylglycine methyl ester (17)

To a solution of methyl N-(1-phenylallyl)carmbate (11) (0.1 g, 0.52 mmol) in CH3CN (3 ml), CICl3 (3 ml), H2O (4.5 ml) was added NaI (0.12 g, 5.23 mmol, 10eq) and RuCl3xH2O (5 mg, 5%). The reaction mixture was stirred at room temperature for 1h, the reaction was poured into CH2Cl2/H2O (10 ml). The organic layer was separated and the aqueous layer was extracted with CH2Cl2 (5ml x 3). The organic was dried over MgSO4 and concentrated. The result dark oil was redissolved in Et2O and filtered through Celite. The solvent was removed and the oil obtained was treated with excess CH3N2 in Et2O at 0 and concentrated. The residue was purified by column chromatography (EtOAc:Hexane=1:3) to afford 0.087 g (74.4%) of 17 as a white solid. RI: 0.26 (EtOAc:hexane=1:3); 1H NMR (500 MHz, CDCl3): δ 7.35-7.30 (m, 5H), 5.95-5.90 (bs, 1H), 5.37 (d, 1H, J=7.5Hz), 3.71 (s, 3H), 3.65 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 172.11, 156.75, 137.35, 129.49, 129.26, 127.87, 58.61, 53.48, 53.10; IR (CH2Cl2): cm⁻¹ 3335, 1747, 1723, 1522; mp: 108–110°C.

N-Methoxycarbonyl phenylalanine methyl ester (18)

Methyl N-(1-benzylallyl)carmbate (13) was converted to 18 as a colorless oil in 70.9% yield. RI: 0.27 (EtOAc:hexane=1:3); 1H NMR (500 MHz, CDCl3): δ 7.30-7.23 (m, 3H), 7.12-7.11 (m, 2H), 5.30-5.20 (bs, 1H), 4.64 (dd, 1H, J=13.5Hz, 6Hz), 3.71 (s, 3H), 3.65 (s, 3H), 3.12 (dd, 1H, J=13.5Hz, 6Hz), 3.07 (dd, 1H, J=13.5Hz, 6Hz); 13C NMR (125 MHz, CDCl3): δ 172.82, 157.01, 136.49, 129.76, 129.30, 127.83, 55.48, 53.01, 52.99, 38.92; IR (neat): cm⁻¹ 3338, 1746, 1722, 1531.

N-Methoxycarbonyl phenylalanine methyl ester (18)

Methyl N-(1-benzylcinnamyl)carmbate (15) was converted to 18 as a colorless oil in 71.3% yield.

N-Cbz-phenylalanine methyl ester (19)

Benzy1 N-(1-benzylcinnamyl)carmbate (16) was converted to 19 as a white solid in 79.4% yield. RI: 0.28 (EtOAc:hexane=1:3); 1H NMR (500 MHz, CDCl3): δ 7.40-7.21 (m, 8H), 7.12-7.10 (m, 2H), 5.30-5.25 (bs, 1H), 5.11 (s, 2H), 4.70 (dd, 1H, J=13.5Hz, 6Hz), 3.73 (s, 3H), 3.15 (dd, 1H, J=13.5Hz, 6Hz), 3.09 (dd, 1H, J=13.5Hz, 6Hz); 13C NMR (125 MHz, CDCl3): δ 172.71, 156.35, 136.96, 136.40, 129.97, 129.84, 129.42, 129.23, 128.89, 128.75, 67.68, 55.53, 53.03, 38.92; IR (CH2Cl2): cm⁻¹ 3340, 1750, 1723, 1520, 1215; mp: 132–135°C.

RESULTS AND DISCUSSION

The preparations of allyl ethers as a starting material of...
Scheme 2. Preparation of allyl ethers

CSI reaction were carried out as shown in scheme 2. Cinnamyl methyl ether (5) was obtained from cinnamyl alcohol (4) by methylation in 92.9% yield. Methyl 4-phenylbut-2-enyl ether (7) was prepared from 4-phenylbut-2-en-1-ol (6) in the same way in 82.2% yields. 6 was oxidized with PCC to give aldehyde 8 which was attacked by phenylmagnesium bromide to afford the alcohol 9 in 59.1% overall yield of two steps. 9 was converted to the corresponding ethers in 78.4% yield for methyl ether 10a and in 67.8% yield for benzyl ether 10b respectively.

Conversions of allyl ethers to the corresponding N-protected allylic amines with CSI were shown in Table I. Initially, we examine the reaction of cinnamyl methyl ether (5) with CSI to afford the internal allylic amine (11) and terminal product (12) as a 1:2.7 mixture of regioisomers and 4-phenylbut-2-enyl methyl ether (7) gave 13 and 14 in a comparable ratio of 1:1.1. In order to improve the isomer ratio of the internal allylic amine, we introduced the phenyl ring at the allylic position in the same direction as the alkoxy moiety. The reaction of 1,4-diphenylbut-2-enyl methyl ether (10a) with CSI gave the only product, methyl N-(1-benzylcinnamyl)carbamate (15), due to the steric hindrance of phenyl ring and the formation of a stable conjugated product (entry 3). In the case of benzyl ethers (10b), the results were similar to those obtained in the methyl case (entry 4). None of the product derived from attack at the benzylic position was observed.

Oxidation of allylic amines with RuCl₃ (Rychnovsky et al., 1992) and esterification with diazomethane gave corresponding N-protected α-amino acid methyl esters. The results were shown in Table II. Allylic amine 11 gave a protected α-phenyl glycine in 74.4% overall yield and 13, 15 and 16 gave the corresponding protected phenyl alanine in 70.9%, 71.3% and 79.4% overall yields respectively.

In conclusion, we developed the novel synthetic method of α-amino acids from allyl ethers using CSI reaction, oxidation and esterification. This synthetic method can be applied to a more complex amino acid formation.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the financial support of the Korea Research Foundation made in the program year 1998.

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### Table I. Conversions of allyl ethers to the corresponding N-protected allylic amines with CSI

<table>
<thead>
<tr>
<th>Allyl Ethers</th>
<th>Allylic amines</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt; (ratio)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>NHCOCH₃</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>NHCOCH₃</td>
</tr>
<tr>
<td>3</td>
<td>10a</td>
<td>NHCOCH₃</td>
</tr>
<tr>
<td>4</td>
<td>10a</td>
<td>NHCOCH₃</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield of pure material

### Table II. Conversions of allylic amines to the corresponding protected α-amino acids

<table>
<thead>
<tr>
<th>Allylic amines</th>
<th>Amino acid methyl esters</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>NHCOCH₃</td>
<td>17</td>
</tr>
<tr>
<td>13</td>
<td>NHCOCH₃</td>
<td>18</td>
</tr>
<tr>
<td>15</td>
<td>NHCOCH₃</td>
<td>19</td>
</tr>
<tr>
<td>16</td>
<td>NHCOCH₃</td>
<td>19</td>
</tr>
</tbody>
</table>

<sup>b</sup>Isolated yield of pure material